Baskar, P.
10/069062

FILE 'REGISTRY' ENTERED AT 11:43:37 ON 11 AUG 2003
E PHOSPHOMEVALONATE KINASE/CN 5
L33 21 S PHOSPHOMEVALONATE KINASE ?/CN

-key terms

L35 1 S 9026-46-4/RN
L36 22 S L33 OR L35

FILE 'HCAPLUS' ENTERED AT 12:18:35 ON 11 AUG 2003
L33 21 SEA FILE=REGISTRY ABB=ON PLU=ON PHOSPHOMEVALONATE KINASE ?/CN
L35 1 SEA FILE=REGISTRY ABB=ON PLU=ON 9026-46-4/RN
L36 22 SEA FILE=REGISTRY ABB=ON PLU=ON L33 OR L35
L37 162 SEA FILE=HCAPLUS ABB=ON PLU=ON L36 OR PMK(S)KINASE OR (PHOSPHOMEVALON? OR PHOSPHO MEVALON? OR PM)(W)KINASE OR MEVALON?(1W)PHOSPHATE KINASE
L38 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L37 AND ALBICAN#

L38 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:152820 HCAPLUS
DOCUMENT NUMBER: 134:204352
TITLE: Cloning, expression, characterization and therapeutic uses of **phosphomevalonate kinase** from Candida **albicans**
INVENTOR(S): Rosamond, John David Charles; Schnell, Norbert Friedemann
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001014533	A2	20010301	WO 2000-GB3100	20000815
WO 2001014533	A3	20010927		
W: JP, MG, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1212431	A2	20020612	EP 2000-951744	20000815
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003507060	T2	20030225	JP 2001-518847	20000815

PRIORITY APPLN. INFO.: GB 1999-19766 A 19990821
WO 2000-GB3100 W 20000815

AB The invention relates to the **phosphomevalonate kinase** (**PMK**) gene (ERG8 gene) from Candida **albicans** (C. **albicans**), to methods for its expression yielding **phosphomevalonate kinase** protein, to novel hybrid organisms for use in such expression methods, to methods for purifn. of the protein, to methods and tools for diagnosing C. **albicans** infection and to assays for identifying inhibitors of the enzyme which inhibitors have potential as anti-fungal agents. The authors have successfully cloned the ERG8 gene from C. **albicans** and detd. its full length nucleotide sequence and corresponding polypeptide sequence. The

coding DNA sequence of the C. **albicans** ERG8 gene isolated is 1299 nucleotides in length and the corresponding protein sequence is 433 amino acids in length.

IT **9026-46-4P, Phosphomevalonate kinase**
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cloning, expression, characterization and therapeutic uses of **phosphomevalonate kinase** from Candida **albicans**)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:20:59 ON 11 AUG 2003)
L39 3 S L38
L40 3 DUP REM L39 (0 DUPLICATES REMOVED)

L40 ANSWER 1 OF 3 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-218441 [22] WPIDS
DOC. NO. CPI: C2001-065267
TITLE: New polypeptides and polynucleotides (ERG8) from Candida **albicans**, useful in assays for identifying inhibitors of **phosphomevalonate kinase** activity and as reagents for diagnosing C. **albicans** infection.
DERWENT CLASS: B04 D16
INVENTOR(S): ROSAMOND, J D C; SCHNELL, N F
PATENT ASSIGNEE(S): (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001014533	A2	20010301	(200122)*	EN	29
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: JP MG US					
EP 1212431	A2	20020612	(200239)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2003507060	W	20030225	(200317)		41

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001014533	A2	WO 2000-GB3100	20000815
EP 1212431	A2	EP 2000-951744	20000815
		WO 2000-GB3100	20000815
JP 2003507060	W	WO 2000-GB3100	20000815
		JP 2001-518847	20000815

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1212431	A2	Based on	WO 200114533
JP 2003507060	W	Based on	WO 200114533

PRIORITY APPLN. INFO: GB 1999-19766 19990821
AN 2001-218441 [22] WPIDS

AB WO 200114533 A UPAB: 20010421
NOVELTY - A purified polypeptide referred to as ERG8 comprising the sequence having 432 amino acids (I) (derived from Candida **albicans**) fully defined in the specification, a sequence possessing at least 80% identity to (I), or an isolated polypeptide of at least 15 contiguous amino acids of the polypeptide above, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an antibody specific for the polypeptide;

(2) a purified polynucleotide (ERG8 gene) comprising:

(a) a nucleotide sequence encoding the polypeptide or a sequence possessing at least 80% identity to it; or

(b) a polynucleotide of at least 15 nucleotides in length, which is capable of specifically hybridizing to a DNA sequence having 547, 577, 1763 or 1299 base pairs (bp) fully defined in the specification, or the complement of these DNA sequences;

(3) an expression vector comprising the polynucleotide;

(4) a host cell containing the expression vector;

(5) a method (M1) for producing the polypeptide;

(6) a method (M2) for identifying compounds that modulate the activity of **phosphomevalonate kinase** (**PMK**) comprising:

(a) contacting a test compound with the polypeptide; and

(b) determining the effect that the test compound has on the activity of the polypeptide;

(7) a compound identified by (M2);

(8) a method (M3) for detecting or diagnosing the presence of C. **albicans** in a test sample comprising contacting the sample with an agent capable of detecting the polypeptide or a sequence possessing at least 80% similarity to it, or a nucleic acid sequence encoding the polypeptide or a sequence possessing at least 80% identity to it; and

(9) a diagnostic kit for detecting the presence of C. **albicans** comprising one or more diagnostic probes and/or diagnostic primers and/or antibodies capable of selectively hybridizing or binding to the polynucleotide or polypeptide

.

USE - The polypeptide (ERG8) is useful in an assay for identifying compounds that inhibit **phosphomevalonate kinase** (**PMK**) activity (claimed). These inhibitors are useful as anti-fungal agents. The polynucleotides and polypeptides are also useful as diagnostic reagents for diagnosing C. **albicans** infection.

Dwg.0/1

L40 ANSWER 2 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2001259704 MEDLINE
DOCUMENT NUMBER: 21140494 PubMed ID: 11243736
TITLE: Nonorthologous gene displacement of **phosphomevalonate kinase.**
AUTHOR: Houten S M; Waterham H R
CORPORATE SOURCE: Department of Pediatrics, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.
SOURCE: MOLECULAR GENETICS AND METABOLISM, (2001 Mar) 72 (3) 273-6.
Journal code: 9805456. ISSN: 1096-7192.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Z74031
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB **Phosphomevalonate kinase** (**PMK**; EC 2.7.4.2) catalyzes the phosphorylation of 5-phosphomevalonate into 5-diphosphomevalonate, an essential step in isoprenoid biosynthesis via the mevalonate pathway. So far, two nonorthologous genes encoding PMK have been described, the Saccharomyces cerevisiae ERG8 gene and the human PMK gene. Here, we report that orthologues of ERG8 are present in eubacteria, fungi, and plants, while orthologues of human PMK are found only in animals, indicative of a nonorthologous gene displacement early in animal evolution. This also is reflected by different consensus ATP-binding motifs: a protein kinase motif in the ERG8 orthologues versus a P-loop or Walker A motif in the animal orthologues. The fact that ERG8 orthologues are found in pathogenic eubacteria and fungi but not in man makes them attractive targets for the development of antibacterial and/or antifungal drugs.

L40 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:189566 SCISEARCH
THE GENUINE ARTICLE: 171YD
TITLE: Biochemistry and molecular biology of sterol synthesis in Saccharomyces cerevisiae
AUTHOR: Lees N D (Reprint); Bard M; Kirsch D R
SOURCE: CRITICAL REVIEWS IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, (18 JAN 1999) Vol. 34, No. 1, pp. 33-47. Publisher: CRC PRESS INC, 2000 CORPORATE BLVD NW, JOURNALS CUSTOMER SERVICE, BOCA RATON, FL 33431. ISSN: 1040-9238.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 96

FILE 'USPATFULL' ENTERED AT 12:21:38 ON 11 AUG 2003
L33 21 SEA FILE=REGISTRY ABB=ON PLU=ON PHOSPHOMEVALONATE KINASE ?/CN
L35 1 SEA FILE=REGISTRY ABB=ON PLU=ON 9026-46-4/RN
L36 22 SEA FILE=REGISTRY ABB=ON PLU=ON L33 OR L35
L37 162 SEA FILE=HCAPLUS ABB=ON PLU=ON L36 OR PMK(S)KINASE OR (PHOSPHOMEVALON? OR PHOSPHO MEVALON? OR PM)(W)KINASE OR MEVALON?(1W)PHOSPHATE KINASE
L41 3 SEA FILE=USPATFULL ABB=ON PLU=ON L37 AND ALBICAN#

L41 ANSWER 1 OF 3 USPATFULL on STN
ACCESSION NUMBER: 2003:215363 USPATFULL
TITLE: Transgenic plants containing altered levels of steroid compounds
INVENTOR(S): Karunanandaa, Balasulojini, St. Louis, MO, UNITED STATES

Post-Beittenmiller, Martha, St. Louis, MO, UNITED STATES
Venkatramesh, Mylavarapu, St. Louis, MO, UNITED STATES
Kishore, Ganesh M., St. Louis, MO, UNITED STATES
Thorne, Gregory M., St. Louis, MO, UNITED STATES
LeDeaux, John R., St. Louis, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003150008	A1	20030807
APPLICATION INFO.:	US 2001-885723	A1	20010620 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-260114P	20010105 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SENNIGER POWERS LEAVITT AND ROEDEL, ONE METROPOLITAN SQUARE, 16TH FLOOR, ST LOUIS, MO, 63102
NUMBER OF CLAIMS: 77
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 78 Drawing Page(s)
LINE COUNT: 5831

AB Disclosed are constructs comprising sequences encoding 3-hydroxy-3methylglutaryl-Coenzyme A reductase and at least one other sterol synthesis pathway enzyme. Also disclosed are methods for using such constructs to alter sterol production and content in cells, plants, seeds and storage organs of plants. Also provided are oils and compositions containing altered sterol levels produced by use of the disclosed constructs. Novel nucleotide sequences useful in the alteration of sterol production are also provided. Also provided are cells, plants, seeds and storage organs of plants comprising sequences encoding 3-hydroxy-3methylglutaryl-Coenzyme A reductase, at least one other sterol synthesis pathway enzyme and at least one tocopherol synthesis enzyme.

INCL INCLM: 800/278.000
INCLS: 536/023.200; 435/189.000; 435/410.000
NCL NCLM: 800/278.000
NCLS: 536/023.200; 435/189.000; 435/410.000

L41 ANSWER 2 OF 3 USPATFULL on STN
ACCESSION NUMBER: 2003:108972 USPATFULL
TITLE: Nucleic acid and amino acid sequences relating to pseudomonas aeruginosa for diagnostics and therapeutics

INVENTOR(S): Rubenfield, Marc J., Framingham, MA, United States
Nolling, Jork, Ouincy, MA, United States
Deloughery, Craig, Medford, MA, United States
Bush, David, Somerville, MA, United States

PATENT ASSIGNEE(S): Genome Therapeutics Corporation, Waltham, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 6551795	B1	20030422
APPLICATION INFO.:	US 1999-252991		19990218 (9)

PRIORITY INFORMATION:	NUMBER	DATE
	US 1998-74788P	19980218 (60)
	US 1998-94190P	19980727 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Allen, Marianne P.
LEGAL REPRESENTATIVE: Burns, Doane, Swecker & Mathis, L.L.P.
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 21431
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides isolated polypeptide and nucleic acid sequences derived from Pseudomonas aeruginosa that are useful in diagnosis and therapy of pathological conditions; antibodies against the polypeptides; and methods for the production of the polypeptides. The invention also provides methods for the detection, prevention and treatment of pathological conditions resulting from bacterial infection.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
INCL INCLM: 435/069.100
INCLS: 536/023.100; 536/023.700; 435/006.000; 435/320.100; 435/253.300; 435/325.000
NCL NCLM: 435/069.100
NCLS: 435/006.000; 435/253.300; 435/320.100; 435/325.000; 536/023.100; 536/023.700

L41 ANSWER 3 OF 3 USPATFULL on STN
ACCESSION NUMBER: 2002:265818 USPATFULL
TITLE: Functionating genomes with cross-species coregulation
INVENTOR(S): Friend, Stephen H., Seattle, WA, UNITED STATES
Stoughton, Roland, San Diego, CA, UNITED STATES
Marton, Matthew J., Seattle, WA, UNITED STATES
He, Yudong, Kirkland, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002146694	A1	20021010
APPLICATION INFO.:	US 2001-779004	A1	20010207 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 3515
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the characterization of genes and their gene products (i.e., proteins). In particular, the invention relates to novel systems and methods for characterizing the

cellular function and/or activity of different cellular constituents such as different genes and/or their gene products. The invention also provides novel systems and methods for comparing different cellular constituents (e.g., novel genes and/or their gene products) from different cells, such as genes and/or gene products from cells of different species of organism or, alternatively, from different cells (e.g., of different cell types or from different tissues types) of the same organism. In particular, using the systems and methods of the invention, it is possible to identify different cellular constituents having common cellular functions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
INCL INCLM: 435/006.000
INCLS: 702/020.000
NCL NCLM: 435/006.000
NCLS: 702/020.000

FILE 'HCAPLUS' ENTERED AT 12:22:24 ON 11 AUG 2003
L42 21 S L37(S)(INHIBIT? OR SUPPRESS? OR MODULAT?)
L43 20 S L42 NOT L38

L43 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:532750 HCAPLUS
DOCUMENT NUMBER: 139:79189
TITLE: Gamete recruitment and developmental competence in mammals by inhibiting de novo sterol biosynthesis and/or promoting sterol efflux
INVENTOR(S): Baltsen, Mogens
PATENT ASSIGNEE(S): Rigshospitalet, Den.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055991	A1	20030710	WO 2002-DK899	20021220

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 2001-1947 A 20011221
AB The invention provides methods for increasing the developmental competence of at least one mammalian germ cell, gamete, zygote, early embryo, implanted blastocyst and/or embryo by administering a compd. which is capable of inhibiting the de novo biosynthesis of sterols and thereby establishing cellular conditions that improve their development and survival. The invention also provides methods

for increasing the sterol efflux prior to fertilization from at least one mammalian ovary, oocyte, female gamete, or ovary-derived cell surrounding an oocyte by administering a compd. which is capable of promoting sterol efflux and thereby reducing the phospholipid/sterol ratio of the cells.

IT **9026-46-4, Phosphomevalonate kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gamete recruitment and developmental competence in mammals by **inhibiting** de novo sterol biosynthesis and/or promoting sterol efflux)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:106581 HCAPLUS
DOCUMENT NUMBER: 138:316663
TITLE: The kinetic mechanism of phosphomevalonate kinase
AUTHOR(S): Pilloff, Daniel; Dabovic, Kristina; Romanowski, Michael J.; Bonanno, Jeffrey B.; Doherty, Mary; Burley, Stephen K.; Leyh, Thomas S.
CORPORATE SOURCE: Department of Biochemistry, The Albert Einstein College of Medicine, Bronx, NY, 10461-1926, USA
SOURCE: Journal of Biological Chemistry (2003), 278(7), 4510-4515
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphomevalonate kinase (I) catalyzes an essential step in the so-called mevalonate pathway, which appears to be the sole pathway for the biosynthesis of sterols and other isoprenoids in mammals and archae. Despite the well-documented importance of this pathway in the cause and prevention of human disease and that it is the biosynthetic root of an enormous diverse class of metabolites, the mechanism of I from any organism has not yet been well-characterized. The 1st structure of a I from Streptococcus pneumoniae was solved recently. The streptococcal enzyme exhibited an atypical P-loop that was a conserved defining feature of the GHMP kinase superfamily. Here, the kinetic mechanism of S. pneumoniae I was characterized in the forward and reverse directions using a combination of classical initial-rate methods including alternate substrate inhibition using ADP.beta.S. The inhibition patterns strongly supported the pattern that in either direction the substrates bound randomly to the enzyme prior to chem., a random sequential bi-bi mechanism. The kinetic consts. were detd. as follows: kcat(forward) = 3.4 s-1, Ki(ATP) = 137 .mu.M, Km(ATP) = 74 .mu.M, Ki(pmev) = 7.7 .mu.M, Km(pmev) = 4.2 .mu.M; kcat(reverse) = 3.9 s-1, Ki(ADP) = 410 .mu.M, Km(ADP) = 350 .mu.M, Ki(ppmev) = 14 .mu.M, Km(ppmev) = 12 .mu.M, where pmev and ppmev represent phosphomevalonate and diphosphomevalonate, resp.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:658670 HCAPLUS
DOCUMENT NUMBER: 137:197518
TITLE: cDNA for squalene biosynthetic enzymes - mevalonate kinase and phosphomevalonate kinase from corp plant and use thereof
INVENTOR(S): Falco, Saverio Carl; Famodu, Omolayo O.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 433,242, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002119546	A1	20020829	US 2001-909745	20010720

PRIORITY APPLN. INFO.: US 1998-107241P P 19981105
US 1999-433242 B2 19991104

AB This invention relates to an isolated nucleic acid fragment encoding squalene biosynthetic enzymes, in particular, mevalonate kinase (claimed) and phosphomevalonate kinase (not claimed) from corn, rice, soybean, and wheat. The invention also relates to the construction of a chimeric gene encoding all or a portion of the above enzymes, in sense or antisense orientation, wherein expression of the chimeric gene results in prodn. of their altered levels in a transformed host cell.

L43 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:391285 HCAPLUS
DOCUMENT NUMBER: 136:381391
TITLE: Phosphomevalonate kinase genes from plants identified by sequence homology and their use in screening for herbicides
INVENTOR(S): Meissner, Ruth; Lechelt-Kunze, Christa
PATENT ASSIGNEE(S): Bayer AG, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10057755	A1	20020523	DE 2000-10057755	20001122
EP 1209236	A1	20020529	EP 2001-126453	20011109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2002355067	A2	20021210	JP 2001-350270	20011115
US 2002123427	A1	20020905	US 2001-988863	20011121

PRIORITY APPLN. INFO.: DE 2000-10057755 A 20001122

AB Plant genes showing sequence homol. to the phosphomevalonate kinase gene ERG8 of Saccharomyces cerevisiae are identified for use in the development of herbicides acting on isoprenoid biosynthesis. The Arabidopsis thaliana **phosphomevalonate kinase** gene was identified by **suppression** subtractive

hybridization.

L43 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:661651 HCAPLUS
DOCUMENT NUMBER: 135:221255
TITLE: Method for screening substance specifically inhibiting non-mevalonate pathway
INVENTOR(S): Seto, Haruo; Kuzuyama, Tomohisa; Mitsui, Nobuo
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064943	A1	20010907	WO 2001-JP1501	20010228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001035995	A5	20010912	AU 2001-35995	20010228
EP 1260590	A1	20021127	EP 2001-908140	20010228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: JP 2000-56753 A 20000302
WO 2001-JP1501 W 20010228

AB An efficient method is provided for screening a substance specifically inhibiting the non-mevalonate pathway by using an organism (e.g., Bacillus) capable of utilizing both of the mevalonate pathway and the non-mevalonate pathway as the pathway for the biosynthesis of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). Thus, a novel method is provided for screening an antimicrobial, a herbicide or an antimalarial capable of specifically **inhibiting** one of the enzyme reactions (e.g., **phosphomevalonate kinase**, diphosphomevalonate decarboxylase, mevalonate kinase, IPP isomerase) on the non-mevalonate pathway for synthesizing IPP and DMAPP without purifying and assaying the enzymes involved.

IT **9026-46-4**, Kinase (phosphorylating), phosphomevalonate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method for screening substance specifically **inhibiting** non-mevalonate pathway)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:640363 HCAPLUS

DOCUMENT NUMBER: 129:258972
TITLE: Identification of tumor-associated alleles of genes essential for cell viability and growth and the development of neoplasm inhibitors targeted against them
INVENTOR(S): Housman, David; Ledley, Fred D.; Stanton, Vincent P., Jr.
PATENT ASSIGNEE(S): Variagenics, Inc., USA
SOURCE: PCT Int. Appl., 605 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9841648	A2	19980924	WO 1998-US5419	19980319
WO 9841648	A3	19990429		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9867643	A1	19981012	AU 1998-67643	19980319
EP 973935	A2	20000126	EP 1998-912974	19980319
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-41057P P 19970320
WO 1998-US5419 W 19980319

AB Strategies for the identification and targeting of specific alleles of genes in the treatment of tumors are described. Tumor-assocd. alleles of genes coding for proteins essential for cell viability or cell growth and that show loss of an alleles in cancer cells due to loss of heterozygosity (LOH) are identified. Inhibitors of the remaining allele, such as antisense nucleic acids or ribozymes, can then be developed. The method can also be used to inhibit the expression of particular alleles of genes for antigens in the control of transplant rejection. Particular categories of appropriate target genes are described, along with specific exemplary genes within those categories and methods of using such target genes. Antisense phosphorothioate oligonucleotides targeting RNA polymerase II and glutamyl/prolyl tRNA synthetase genes were tested for cytotoxicity in vitro. Oligonucleotides with a single base mismatch were significantly less toxic than those without mismatches. A no. of genes essential for proliferation were mapped and shown to be affected by loss-of-heterozygosity in oncogenesis.

IT **9026-46-4**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibition** of expression of tumor-assocd. alleles of genes for; identification of tumor-assocd. alleles of essential genes and development of neoplasm **inhibitors** targeted against them)

L43 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:755756 HCAPLUS
DOCUMENT NUMBER: 128:99220
TITLE: Post-translational regulation of mevalonate kinase by intermediates of the cholesterol and nonsterol isoprene biosynthetic pathways
AUTHOR(S): Hinson, Debra D.; Chambliss, Ken L.; Toth, Matthew J.; Tanaka, Richard D.; Gibson, K. Michael
CORPORATE SOURCE: Inst. Metabolic Disease, Baylor Univ. Medical Center, Dallas, TX, 75226, USA
SOURCE: Journal of Lipid Research (1997), 38(11), 2216-2223
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To access the potential for feedback **inhibition** by isoprene intermediates in the cholesterol and nonsterol isoprene biosynthetic pathway, we expressed human cDNAs encoding mevalonate kinase (MKase), **phosphomevalonate kinase** (PMKase), and mevalonate diphosphate decarboxylase (MDDase) as fusion proteins in Escherichia coli DH5.alpha., and purified these proteins by affinity chromatog. Several phosphorylated and non-phosphorylated isoprenes were analyzed as inhibitors of the enzymes using a std. spectrophotometric assay. Of the three proteins, only MKase was inhibited through competitive interaction at the ATP-binding site. The intermediates studied (and their relative inhibitory capacity) were: geranylgeranyl-diphosphate (GGPP, C20) > farnesyl-diphosphate (FPP,C15) > geranyl-diphosphate (GPP,C10) > isopentenyl-diphosphate (IPP, C5) .gtoreq. 3,3-dimethylallyl-diphosphate (DMAPP, C5) > farnesol (C15) > dolichol-phosphate (DP, C80-100). Mevalonate-diphosphate, geraniol, and dolichol were not inhibitors. Our data further define the spectrum of physiol. inhibitors of MKase, and provide the first evidence for feedback inhibition of MKase by a nonsterol isoprene produced by the branched pathway, dolichol-phosphate. These results provide addnl. evidence that MKase may occupy a central regulatory role in the control of cholesterol and nonsterol isoprene biosynthesis.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:488167 HCAPLUS
DOCUMENT NUMBER: 115:88167
TITLE: Effect of phenylalanine derivatives on the main regulatory enzymes of hepatic cholesterogenesis
AUTHOR(S): Castillo, M.; Martinez-Cayuela, M.; Zafra, M. F.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem. Mol. Biol., Univ. Granada, Granada, 18071, Spain
SOURCE: Molecular and Cellular Biochemistry (1991), 105(1), 21-5
CODEN: MCBIB8; ISSN: 0300-8177
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phenylalanine, phenylpyruvate, and phenylacetate produced

considerable **inhibition** of chick liver mevalonate 5-pyrophosphate decarboxylase, while mevalonate kinase and **mevalonate** 5-**phosphate kinase** were not significantly affected. Phenolic derivs. of phenylalanine produced a similar inhibition of decarboxylase activity as that found in the presence of Ph metabolites. The degree of inhibition increased with increasing concns. of inhibitors (1.25-5.00 mM). Simultaneous supplementation of different metabolites in conditions similar to those in exptl. phenylketonuria (0.25 mM each) produced a clear inhibition of liver decarboxylase and 3-hydroxy-3-methylglutaryl-CoA reductase. This is the first report on the in vitro inhibition of both liver regulatory enzymes of cholesterogenesis in phenylketonuria-like conditions. The results show a lower inhibition of decarboxylase than that of reductase but suggest an important regulatory role of decarboxylase in cholesterol synthesis.

L43 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:140916 HCAPLUS
DOCUMENT NUMBER: 114:140916
TITLE: Inhibition of chick brain cholesterogenic enzymes by phenyl and phenolic derivatives of phenylalanine
AUTHOR(S): Castillo, M.; Iglesias, J.; Zafra, M. F.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem. Mol. Biol., Univ. Granada, Granada, 18071, Spain
SOURCE: Neurochemistry International (1991), 18(2), 171-4
CODEN: NEUIDS; ISSN: 0197-0186
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phenylalanine and its Ph metabolites produced a clear **inhibition** of chick brain mevalonate 5-pyrophosphate decarboxylase, while mevalonate kinase and **mevalonate** 5-**phosphate kinase** were not significantly affected. Phenolic derivs. produced a similar or higher inhibition than that found in the presence of Ph metabolites. The inhibition was progressive with increasing concns. of inhibitors (1.25-5.00 mM). Phenylpyruvate and p-hydroxyphenyl-lactate were the most potent inhibitors of decarboxylase activity. Simultaneous supplementation of each metabolite at 0.25 mM concn. produced a considerable inhibition of brain decarboxylase and 3-hydroxy-3-methylglutaryl-CoA reductase. This is the first report on the in vitro inhibition of both brain regulatory enzymes of cholesterogenesis in phenylketonuric-like conditions.

L43 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:2210 HCAPLUS
DOCUMENT NUMBER: 114:2210
TITLE: Site of clomazone action in tolerant-soybean and susceptible-cotton photomixotrophic cell suspension cultures
AUTHOR(S): Norman, Michael A.; Liebl, Rex A.; Widholm, Jack M.
CORPORATE SOURCE: Dep. Agron., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Plant Physiology (1990), 94(2), 704-9
CODEN: PLPHAY; ISSN: 0032-0889

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies were conducted to det. the herbicidal site of clomazone (I) action in tolerant-soybean (Glycine max. cv Corsoy) (SB-M) and susceptible-cotton (Gossypium hirsutum cv Stoneville 825) (COT-M) photomixotrophic cell suspension cultures. Although a 10 .mu.m I treatment did not significantly reduce the terpene or mixed terpenoid content (.mu.g/g fresh wt.) of the SB-M cell line, there was over a 70% redn. in the chlorophyll (Chl), carotenoid (CAR), and plastoquinone (PQ) content of the COT-M cell line. The tocopherol (TOC) content was reduced only 35.6%. Redns. in the levels of Chl, CAR, TOC, and PQ indicate that the site of I action in COT-M cells is prior to geranylgeranyl pyrophosphate (GGPP). The I treatment did not significantly reduce the low of [14C]mevalonate ([14C]MEV) (nanocuries per g fresh wt.) into CAR and the 3 mixed terpenoid compds. of SB-M cells. Conversely, [14C]MEV incorporation into CAR and the terpene moieties of Chl, PQ, and TOC in COT-M cells was reduced at least 73%, indicating that the site of I action must be after MEV. Sequestration of I away from the chlorplast cannot account for soybean tolerance to I since chloroplasts isolated from both cell lines incubated with [14C]I contained a similar amt. of radioactivity (disintegrations per min per .mu.g of Chl). The possible site(s) of I **inhibition** include mevalonate kinase, **phosphomevalonate kinase,** pyrophosphomevalonate decarboxylase, isopentenyl pyrophosphate isomerase, and/or a prenyl transferase.

L43 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:111855 HCAPLUS
DOCUMENT NUMBER: 112:111855
TITLE: Effects of clofibrate on the main regulatory enzymes of cholesterogenesis
AUTHOR(S): Castillo, M.; Burgos, C.; Rodriguez-Vico, F.; Zafra, M. F.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem. Mol. Biol., Univ. Granada, Granada, 18071, Spain
SOURCE: Life Sciences (1990), 46(6), 397-403
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The in vivo effect of clofibrate on the main regulatory enzymes of cholesterogenesis was comparatively studied for the first time in chick liver and brain. 3-Hydroxy-3-methylgutaryl-CoA reductase and mevalonate 5-pyrophosphate decarboxylase from chick liver were **inhibited** by this hypocholesterolemic drug, while mevalonate kinase and **mevalonate** 5-**phosphate kinase** were not affected. No enzyme from chick brain was inhibited by the in vivo treatment. However, both liver and brain reductase activity was inhibited by clofibrate, in a concn.-dependent (1.25-5.00 mM) manner.

L43 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1987:526901 HCAPLUS
DOCUMENT NUMBER: 107:126901
TITLE: Effect of clofibrate on brain mevalonate-5-pyrophosphate decarboxylase
AUTHOR(S): Zafra, M. F.; Riquelme, S.; Castillo, M.; Garcia-Peregrin, E.

CORPORATE SOURCE: Dep. Biochem., Univ. Granada, Granada, Spain
SOURCE: Neurochemical Research (1987), 12(9), 787-90
CODEN: NEREDZ; ISSN: 0364-3190
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of clofibrate on the activity of the 3 mevalonate-activating enzymes has been studied for the 1st time in brain by reactions carried out using [2-14C] mevalonic acid as substrate and 105,000 g supernatants from 14-day-old chick brain. Mevalonate-5-pyrophosphate decarboxylase was clearly **inhibited**, while mevalonate kinase and **mevalonate -5-phosphate kinase** were not affected. The effect of clofibrate on decarboxylase activity was progressive with increasing concns. (1.25-5.00 mM) of the inhibitor. A transient inhibition and a subsequent activation as a function of clofibrate concn. seemed to occur for mevalonate kinase. Direct measurements of decarboxylase activity utilizing [2-14C] pyrophosphomevalonate as the specific substrate of this enzyme corroborated these results. Kinetic studies showed that clofibrate competes with the substrate ATP.

L43 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1986:147667 HCAPLUS
DOCUMENT NUMBER: 104:147667
TITLE: Effects of different nutritional conditions on chick liver mevalonate-activating enzymes
AUTHOR(S): Gonzalez-Pacanowska, D.; Marco, C.; Garcia-Martinez, J.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem., Univ. Granada, Granada, Spain
SOURCE: Biochimica et Biophysica Acta (1986), 875(3), 605-9
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The response of mevalonate kinase [9026-52-2], mevalonate 5-phosphate kinase [9026-46-4], and mevalonate 5-pyrophosphate decarboxylase [9024-66-2] of chick liver to different dietary situations was investigated. Fasting **inhibited** mevalonate kinase and mevalonate 5-pyrophosphate decarboxylase activities, while **mevalonate 5-phosphate kinase** remained practically unaltered. Refeeding after 72 h of starvation restored mevalonate kinase activity to normal levels after 120 h of refeeding. Likewise, decarboxylase activity reached normal levels at 72 h of refeeding the std. diet and slightly supranormal levels after 120 h. In addn., the sequential response of the 3 enzymes to a high cholesterol [57-88-5] diet was followed throughout a 120-h period. Feeding a 5% cholesterol diet to 13-day-old chicks previously fed with a std. diet from hatching reduced considerably the activity of mevalonate 5-pyrophosphate decarboxylase, while the kinases were less affected. The present results support the idea of a coordinate regulation of the enzymes implied in cholesterol biosynthesis and suggest that mevalonate 5-pyrophosphate decarboxylase may play a significant role in this regulation.

L43 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1986:122925 HCAPLUS
DOCUMENT NUMBER: 104:122925
TITLE: Effect of clofibrate on mevalonate-activating

enzymes from chick liver
AUTHOR(S): Zafra, M. F.; Castillo, M.; Riquelme, S.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem., Univ. Granada, Granada, Spain
SOURCE: IRCS Medical Science (1985), 13(12), 1249-50
CODEN: IMSCE2; ISSN: 0268-8220
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Direct addn. of 3 mM clofibrate [637-07-0] to the reaction mixt. produced an **inhibition** of mevalonate 5-pyrophosphate decarboxylase (MVAPP decarboxylase) [9024-66-2], but did not affect mevalonate kinase (MVA kinase) [9026-52-2] and **mevalonate5 -phosphate kinase** (MVAP kinase) [**9026-46-4**] activities from chick liver; preincubation of MVAPP decarboxylase with clofibrate for 10 min increased the **inhibition**. Only high concns. of clofibrate (5.00 mM) preincubated with the enzyme were able to inhibit MVA kinase and MVAP kinase. A noncompetitive mechanism with ATP was found in the inhibition of MVAPP decarboxylase by clofibrate.
IT **9026-46-4**
RL: PROC (Process)
(**inhibition** of, by clofibrate, of liver)

L43 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1985:146429 HCAPLUS
DOCUMENT NUMBER: 102:146429
TITLE: Role of mevalonate-5-pyrophosphate decarboxylase in the regulation of chick intestinal cholesterogenesis
AUTHOR(S): Gonzalez-Pacanowska, D.; Marco, C.; Garcia-Martinez, J.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem., Univ. Granada, Granada, Spain
SOURCE: Biochimica et Biophysica Acta (1985), 833(3), 449-55
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The response to different dietary conditions of the enzymes responsible for the transformation of mevalonic acid to isopentenyl pyrophosphate was studied in the small bowel of the chick to elucidate the role of these enzymes in the regulation of intestinal cholesterogenesis. Feeding a 2% cholesterol diet from hatching resulted in a small **inhibition** of mevalonate 5-pyrophosphate decarboxylate (I), whereas mevalonate kinase and **mevalonate** 5-**phosphate kinase** remained unaltered. Similar results were obtained for the 3 enzymes when 13-day-old chicks fed a std. fat-free diet were switched to a 5% cholesterol diet. Starved chicks exhibited lower intestinal I activity than chicks fed a std. diet; refeeding resulted in levels of activity similar to or slightly greater than controls. None of the enzyme effecting the conversion of mevalonate to isopentenyl pyrophosphate in the small intestine presented diurnal variations. I may play a significant role in the regulation of cholesterol synthesis in the small intestine.

L43 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1985:77668 HCAPLUS
DOCUMENT NUMBER: 102:77668

TITLE: Feedback **inhibition** of mevalonate kinase, **mevalonate**-5-**phosphate kinase** and mevalonate-5-pyrophosphate decarboxylase by cholesterol feeding
AUTHOR(S): Gonzalez-Pacanowska, D.; Marco, C.; Garcia-Martinez, J.; Linares, A.; Garcia-Peregrin, E.
CORPORATE SOURCE: Dep. Biochem., Univ. Granada, Granada, Spain
SOURCE: Nutrition Reports International (1985), 31(1), 121-7
CODEN: NURIBL; ISSN: 0029-6635
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Liver and brain phosphorylation and decarboxylation of mevalonic acid [150-97-0] was measured during the early stages of postnatal development in chicks fed from hatching a diet contg. 2% cholesterol [57-88-5]. Hepatic phosphorylation and decarboxylation of mevalonate was significantly inhibited after 2 wk of treatment although mevalonate-5-pyrophosphate decarboxylase [9024-66-2] appeared to be more sensitive than the phosphorylating enzymes to the presence of cholesterol in the diet. Direct measurements of decarboxylase activity utilizing the specific substrate of this enzyme corroborated these results, showing that after 2 wk of treatment only a 25% of control activity was found in chicks fed a cholesterol supplemented diet. On the other hand, brain enzymic activities remained unaltered under similar conditions of a cholesterol diet. These results suggest that reactions responsible for the conversion of mevalonate to isopentenyl pyrophosphate [358-71-4] and esp. that catalyzed by mevalonate-5-pyrophosphate decarboxylase may play an important role in the suppression of cholesterogenesis subsequent to cholesterol feeding.

L43 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1980:2231 HCAPLUS
DOCUMENT NUMBER: 92:2231
TITLE: **Inhibition** of rat liver mevalonate pyrophosphate decarboxylase and **mevalonate phosphate kinase** by phenyl and phenolic compounds
AUTHOR(S): Bhat, Charavu Shama; Ramasarma, T.
CORPORATE SOURCE: Dep. Biochem., Indian Inst. Sci., Bangalore, 560 012, India
SOURCE: Biochemical Journal (1979), 181(1), 143-51
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rat liver mevalonate pyrophosphate decarboxylase (EC 4.1.1.33) and **mevalonate phosphate kinase** (EC 2.7.4.2) were **inhibited** by various Ph and phenolic acids. Compds. with the phenyl-vinyl structure were more effective. Kinetic studies showed that some phenolic acids competed with the substrates, mevalonate 5-phosphate and mevalonate 5-pyrophosphate, whereas others inhibited uncompetitively. Di- and trihydroxyphenyl compds. and p-chlorophenoxyisobutyrate, a hypocholesterolemic drug, had no effect on these enzymes. Of these 2 enzymes and mevalonate kinase (EC 2.7.1.36), mevalonate pyrophosphate decarboxylase had the lowest specific activity and is probably the rate-detg. step in this path.

IT **9026-46-4**
RL: BIOL (Biological study)
(**inhibition** of liver, by Ph and phenolic compds.)

L43 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1979:570587 HCAPLUS
DOCUMENT NUMBER: 91:170587
TITLE: Effect of phenyl and phenolic acids on mevalonate-5-phosphate kinase and mevalonate-5-pyrophosphate decarboxylase of the rat brain
AUTHOR(S): Bhat, Charavu Shama; Ramasarma, T.
CORPORATE SOURCE: Dep. Biochem., Indian Inst. Sci., Bangalore, India
SOURCE: Journal of Neurochemistry (1979), 32(5), 1531-7
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ph and phenolic acids **inhibited** metab. of mevalonate in rat brain by **inhibition** of mevalonate 5-pyrophosphate decarboxylase (EC 4.1.1.33) (I); phenolic acids also **inhibited mevalonate** 5-**phosphate kinase** (EC 2.7.4.2) (II) on preincubation. Inhibition kinetics showed that p-coumaric and isoferulic acids competed with the substrates, mevalonate 5-phosphate or mevalonate 5-pyrophosphate, whereas other acids showed a noncompetitive type of inhibition. Chlorophenoxyisobutyrate did not affect I or II.

L43 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1979:68385 HCAPLUS
DOCUMENT NUMBER: 90:68385
TITLE: **Inhibition** of 5-**phosphomevalonate kinase** by an isosteric analog of 5-phosphomevalonate
AUTHOR(S): Popjak, George; Parker, Thomas S.; Sarin, Vivander; Tropp, Burton E.; Engel, Robert
CORPORATE SOURCE: Sch. Med., Univ. California, Los Angeles, CA, USA
SOURCE: Journal of the American Chemical Society (1978), 100(25), 8014
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rat liver 10,000g supernatant contg. **phosphomevalonate kinase** (I) was **inhibited** by 3-hydroxy-3-methyl-6-phosphohexanoic acid (II), an isosteric analog of the substrate, 5-phosphomevalonic acid. The apparent Ki for racemic II was 145 .mu.M. II was not a substrate for I as there was no evidence of phosphorylation of II.
IT **9026-46-4**
RL: PROC (Process)
(**inhibition** of, of liver, by hydroxymethylphosphohexanoic acid)

L43 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1966:106229 HCAPLUS
DOCUMENT NUMBER: 64:106229
ORIGINAL REFERENCE NO.: 64:20081c

TITLE: Phosphomevalonate kinase from Hevea brasiliensis latex
AUTHOR(S): Skilleter, D. N.; Williamson, I. P.; Kekwick, R. G. O.
CORPORATE SOURCE: Univ. Birmingham, UK
SOURCE: Biochemical Journal (1966), 98(2), 27P
CODEN: BIJOAK; ISSN: 0264-6021
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A method of isolating a prepn. of phosphomevalonate kinase (I) (free from pyrophosphomevalonate decarboxylase) from freeze-dried latex serum is described. I catalyzes the phosphorylation of 5-phosphomevalonate to 5-pyrophosphomevalonate in the presence of ATP. I has a pH optimum of 7.0-7.5; max. activity occurs at 40.degree.; the enzyme requires Mg2+ or Mn2+ and thiol compds.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:23:53 ON 11 AUG 2003)
L44 58 SEA ABB=ON PLU=ON L42
L45 16 SEA ABB=ON PLU=ON L44 AND (POLYPROTEIN OR PROTEIN OR PEPTIDE OR POLYPEPTIDE)
L46 17 SEA ABB=ON PLU=ON L44 AND (DETERM? OR DETECT? OR DET## OR SCREEN? OR ASSAY? OR DIAGNOS? OR TEST?)
L47 23 SEA ABB=ON PLU=ON (L45 OR L46) NOT L39
L48 16 DUP REM L47 (7 DUPLICATES REMOVED)

L48 ANSWER 1 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
ACCESSION NUMBER: 2003269827 EMBASE
TITLE: The kinetic mechanism of phosphomevalonate kinase.
AUTHOR: Pilloff D.; Dabovic K.; Romanowski M.J.; Bonanno J.B.; Doherty M.; Burley S.K.; Leyh T.S.
CORPORATE SOURCE: T.S. Leyh, Dept. of Biochemistry, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461-1926, United States. leyh@aecom.yu.edu
SOURCE: Journal of Biological Chemistry, (14 Feb 2003) 278/7 (4510-4515).
Refs: 39
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Phosphomevalonate kinase** catalyzes an essential step in the so-called mevalonate pathway, which appears to be the sole pathway for the biosynthesis of sterols and other isoprenoids in mammals and archea. Despite the well documented importance of this pathway in the cause and prevention of human disease and that it is the biosynthetic root of an enormous diverse class of metabolites, the mechanism of **phosphomevalonate kinase** from any organism is not yet well characterized. The first structure of a **phosphomevalonate kinase** from Streptococcus pneumoniae was solved recently. The enzyme exhibits an atypical P-loop that is a conserved defining feature of the GHMP kinase superfamily. In this study, the kinetic mechanism of the S. pneumoniae enzyme is characterized in the forward and reverse directions using a combination of classical initial-rate methods including alternate substrate **inhibition** using ADP.beta.S.

The **inhibition** patterns strongly support that in either direction the substrates bind randomly to the enzyme prior to chemistry, a random sequential bi-bi mechanism. The kinetic constants are as follows: k(cat(forward)) = 3.4 s(-1), K(i(ATp)) = 137 .mu.M, K(m(ATP)) = 74 .mu.M, K(i(pmev)) = 7.7 .mu.M, K(m(pmev)) = 4.2 .mu.M; k(cat(reverse)) = 3.9 s(-1), K(i(ADP)) = 410 .mu.M, K(m(ADP)) = 350 .mu.M, K(i(ppmev)) = 14 .mu.M, K(m(ppmev)) = 12 .mu.M, where pmev and ppmev represent phosphomevalonate and diphosphomevalonate, respectively.

L48 ANSWER 2 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-548086 [58] WPIDS
CROSS REFERENCE: 2002-537944 [57]; 2002-643302 [69]
DOC. NO. CPI: C2002-155486
TITLE: Production of prenyl alcohols by culturing translationally-active mutated cells with reduced squalene synthase gene to express less transcriptional product.
DERWENT CLASS: B04 D16 E17
INVENTOR(S): OBATA, S; OHTO, C
PATENT ASSIGNEE(S): (TOYT) TOYOTA JIDOSHA KK
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002053747	A1	20020711	(200258)*	JA	262
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
W: CA US					
JP 2003088368	A	20030325	(200330)		96

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002053747	A1	WO 2001-JP11215	20011220
JP 2003088368	A	JP 2001-282978	20010918

PRIORITY APPLN. INFO: JP 2001-282978 20010918; JP 2000-401701 20001228; JP 2000-403067 20001228
AN 2002-548086 [58] WPIDS
CR 2002-537944 [57]; 2002-643302 [69]
AB WO 200253747 A UPAB: 20030513
NOVELTY - A method for producing prenyl alcohol comprises culturing mutated cells, having been mutated so as to reduce the amount of transcriptional product of squalene synthase gene transcriptional activity, and then collecting prenyl alcohol from the culture medium.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a similar method by culturing mutated cells which are transformants obtained by transferring a recombinant DNA for expression that contains the IPP (isopentenyl diphosphate) synthesis pathway-associated enzyme or genome integration DNA; or by culturing under transcription-**inhibitory** conditions mutated cells wherein the transcriptional promoter domain of the squalene synthase has been substituted by a transcription-**inhibitory**

promoter to reduce the amount of transcription product; or culturing under transcription-**inhibitory** conditions the recombinant cells obtained by carrying out both transformation above; and

(2) mutated cells obtained by using any of the recombination methods.

USE - The method is for the production of prenyl alcohols, which is for use in industrial synthesis of isoprenoid-terpenoid compounds particularly physiologically-active prenyl alcohol geometric isomers.

ADVANTAGE - The method can be operated on large scale.

Dwg.0/36

L48 ANSWER 3 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-445508 [48] WPIDS
DOC. NO. CPI: C2002-127024
TITLE: New nucleic acid encoding plant **phosphomevalonate kinase**, useful for identifying **modulators**, potentially useful as herbicides and growth regulators.
DERWENT CLASS: C06 D16
INVENTOR(S): LECHELT-KUNZE, C; MEISSNER, R
PATENT ASSIGNEE(S): (FARB) BAYER AG; (LECH-I) LECHELT-KUNZE C; (MEIS-I) MEISSNER R
COUNTRY COUNT: 28
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 10057755	A1	20020523	(200248)*		17
EP 1209236	A1	20020529	(200248)	GE	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2002123427	A1	20020905	(200260)		
JP 2002355067	A	20021210	(200311)		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 10057755	A1	DE 2000-10057755	20001122
EP 1209236	A1	EP 2001-126453	20011109
US 2002123427	A1	US 2001-988863	20011121
JP 2002355067	A	JP 2001-350270	20011115

PRIORITY APPLN. INFO: DE 2000-10057755 20001122
AN 2002-445508 [48] WPIDS
AB DE 10057755 A UPAB: 20020730

NOVELTY - A nucleic acid (I) that encodes a plant **phosphomevalonate kinase** (PMVK), excluding the known fully defined partial sequences (S3-5) of 611, 728 and 571 base pairs as given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) DNA construct (DC) comprising (I) and a heterologous promoter;

(b) vector containing (I) or DC;

(c) host cell containing (I), DC or the vector of (b);

(d) **polypeptide** (II) with PMVK activity encoded by (I);
(e) antibody (Ab) that binds specifically to (II);
(f) preparing (I) or (II);
(g) identifying compounds (A) that bind to and/or **modulate** activity of (II);
(h) identifying compounds (B) that alter expression of (II); and
(i) (A), (B) and herbicides identified by methods (g) and (h).
ACTIVITY - Herbicide. No details of **tests** for herbicidal activity are given.
MECHANISM OF ACTION - **Inhibition** of **phosphomevalonate kinase.**
USE - Plant PMVK, (I) and constructs and host cells that contain (I), are used to identify agents that bind to and/or **modulate** activity of PMVK, potentially useful as herbicides and growth regulators. (I) is also used for recombinant production of PMVK.
Dwg.0/1

L48 ANSWER 4 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-071392 [08] WPIDS
DOC. NO. CPI: C2001-020029
TITLE: New isolated mevalonate pathway gene polynucleotide derived from bacterium is useful for treatment of bacterial infection.
DERWENT CLASS: B04 D16
INVENTOR(S): BROWN, J R; GWYNN, M; MATHIE, T B; MYERS, J E; TRAINI, C M; VAN HORN, S; WILDING, E I
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP; (SMIK) SMITHKLINE BEECHAM PLC
COUNTRY COUNT: 19
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000078935	A1	20001228	(200108)*	EN	158

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: JP

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000078935	A1	WO 2000-US17262	20000622

PRIORITY APPLN. INFO: US 1999-146682P 19990802; US 1999-140519P 19990622
AN 2001-071392 [08] WPIDS
AB WO 200078935 A UPAB: 20010207
NOVELTY - An isolated mevalonate pathway gene polynucleotide (I) derived from a bacterium comprised within the clade of Class II of the phylogenetic tree of figure 1 of the specification, is new.
(Editors Note: Figures are referred to in the claims but no figures are provided in the specification.)
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated mevalonate pathway gene **polypeptide** (II) encoded by (I);

(2) a mevalonate pathway gene family polynucleotide (III);

(3) a polynucleotide encoding 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase (MevA), HMGCoA synthase (PksG), mevalonate diphosphate decarboxylase (MevD) or mevalonate kinases (MevK), including mevalonate kinase (MevK1) and **phosphomevalonate kinase** (MevK2), isolated from Streptococcus, especially S. pyogenes or S. pneumoniae, Staphylococcus, especially S. aureus, S. epidermidis or S. haemolyticus, Enterococcus, especially E. faecalis or E. faecium, PksG may also be isolated from Staphylococcus carnosus;

(4) polynucleotides encoding a mevalonate pathway family **polypeptide** falling within the clade defined by nodes A-F of figure 1, nodes A-G of figure 2, nodes A-E of figure 3 and nodes A-N of figure 4 of the specification;

(5) producing (II) comprising culturing a host cell, where (II) is selected from:

(a) an isolated **polypeptide** comprising an amino acid sequence having at least 95% identity to one of the 36, 292-813 amino acid sequences given in the specification;

(b) an isolated **polypeptide** comprising or is one of the 36, 292-813 amino acid sequences given in the specification; and

(c) a **polypeptide** that is encoded by a recombinant polynucleotide comprising one of the 36, 879-2442 base pair (bp) sequences, given in the specification;

(6) producing a host cell comprising (a membrane of) an expression system expressing (II);

(7) a host cell or membrane (IV) expressing (II);

(8) an antibody immunospecific for (II); and

(9) **screening** to identify compounds that agonize or **inhibit** the function of (II) comprising:

(a) measuring the binding of a candidate compound to the **polypeptide** (or to the cells or membranes bearing the **polypeptide**) or a fusion **protein** by a **detecting** a label directly or indirectly associated with the candidate compound;

(b) measuring the binding of a candidate compound to the **polypeptide** (or to the cells or membranes bearing the **polypeptide**) or a fusion **protein** in the presence of a labelled competitor;

(c) **testing** whether the candidate compound results in a signal generated by activation or **inhibition** of the **polypeptide** using **detection** systems appropriate to the cells or cell membranes bearing the **polypeptide**;

(d) mixing a candidate compound with a solution comprising a **polypeptide** to form a mixture, measuring the activity of the **polypeptide** and comparing the activity to a standard; or

(e) **detecting** the effect of a candidate compound on the production of mRNA encoding the **polypeptide** using, e.g. enzyme linked immunosorbant **assay** (ELISA).

(Editors Note: Figures are referred to in the claims but no figures are provided in the specification.)

ACTIVITY - Antibacterial.

No supporting biological data given.

MECHANISM OF ACTION - 3-hydroxy-3-methylglutaryl CoA (HMGCoA) active.

USE - For treatment of disease related to bacterial infection,

e.g. conjunctivitis, pneumonia, bacteremia and meningitis.
ADVANTAGE - This treatment is effective against drug resistant bacteria.
Dwg.0/4

L48 ANSWER 5 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-302839 [26] WPIDS
CROSS REFERENCE: 2000-126928 [11]; 2000-126929 [11]; 2000-147377 [13]; 2002-074192 [10]
DOC. NO. CPI: C2000-091732
TITLE: Production of alpha-tocopherol compounds, useful for production of vitamin E compounds for use as nutritional supplements in humans and animals, from geranylgeraniol.
DERWENT CLASS: B02 D16 E13
INVENTOR(S): HYATT, J A; MAURINA-BRUNKER, J; MCMULLIN, T W; MILLIS, J R; SAUCY, G G
PATENT ASSIGNEE(S): (DCVB-N) DCV INC DBA BIO-TECH RESOURCES; (EACH) EASTMAN CHEM CO; (DCVD-N) DCV INC
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000001649	A1	20000113	(200026)*	EN	202
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW					
AU 9948629	A	20000124	(200027)		
EP 1095001	A1	20010502	(200125)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
US 6242227	B1	20010605	(200133)		
JP 2002519397	W	20020702	(200246)		171

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000001649	A1		WO 1999-US15262	19990706
AU 9948629	A		AU 1999-48629	19990706
EP 1095001	A1		EP 1999-932294	19990706
			WO 1999-US15262	19990706
US 6242227	B1	Provisional	US 1998-91868P	19980706
			US 1999-352654	19990706
JP 2002519397	W		WO 1999-US15262	19990706
			JP 2000-558055	19990706

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9948629	A	Based on	WO 200001649
EP 1095001	A1	Based on	WO 200001649
JP 2002519397	W	Based on	WO 200001649

PRIORITY APPLN. INFO: US 1998-91868P 19980706; US 1999-352654 19990706
AN 2000-302839 [26] WPIDS
CR 2000-126928 [11]; 2000-126929 [11]; 2000-147377 [13]; 2002-074192 [10]
AB WO 200001649 A UPAB: 20020722
NOVELTY - Producing alpha -tocopherol (aT) from biologically produced geranylgeraniol (GG) comprises selective oxidation, hydrogenation, deoxygenation and reaction of the produced phytol and isophytol mixture with trimethylhydroquinone.
DETAILED DESCRIPTION - Preparation of alpha-tocopherol or its esters comprises:
(a) biologically producing geranylgeraniol (GG); and
(b) chemically converting the GG into aT or an aT ester by a process comprising:
(i) selectively oxidizing the 2,3-carbon-carbon double bond in GG to produce GG-2,3-epoxide;
(ii) hydrogenating the 3 remaining C-C double bonds in the epoxide to produce epoxyphytol;
(iii) deoxygenating the epoxyphytol to produce a mixture of phytol and isophytol by reaction with an oxygen acceptor; and
(iv) reacting the phytol and isophytol mixture with trimethylhydroquinone to produce aT.
INDEPENDENT CLAIMS are also included for:
(1) a method for producing aT from GG comprising steps (b) (i)-(iv) as in (A);
(2) a method for producing a mixture of phytol and isophytol comprising reacting epoxyphytol with an oxygen acceptor in the presence of a substituted rhenium trioxide catalyst;
(3) a method for preparing gamma -tocopherol (gT) which comprises catalytic hydrogenation of 4-chromanone tocotrienol.
USE - The methods can be used for the production of vitamin E (d-aT), useful as a nutritional supplement in humans and animals.
ADVANTAGE - The processes are more efficient
Dwg.0/0

L48 ANSWER 6 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 1
ACCESSION NUMBER: 1999:6982 BIOSIS
DOCUMENT NUMBER: PREV199900006982
TITLE: **Protein**-kinase-Cmu expression correlates with enhanced keratinocyte proliferation in normal and neoplastic mouse epidermis and in cell culture.
AUTHOR(S): Rennecke, Joerge; Rehberger, Petra Andrea; Fuerstenberger, Gerhard; Johannes, Franz-Josef; Stoehr, Michael; Marks, Friedrich; Richter, Karl Hartmut (1)
CORPORATE SOURCE: (1) DKFZ-B0500, INF 280, D-69120 Heidelberg Germany
SOURCE: International Journal of Cancer, (Jan. 5, 1999) Vol. 80, No. 1, pp. 98-103.
ISSN: 0020-7136.
DOCUMENT TYPE: Article
LANGUAGE: English
AB In order to gain insight into the biological function of a PKC iso-enzyme, the **protein kinase** Cmu, we analyzed the expression pattern of this **protein** in mouse epidermis and keratinocytes in culture. Daily analysis of neonatal mouse

epidermis immediately after birth showed a time-dependent reduction in the PKCmu content. Expression of the proliferating-cell nuclear antigen (PCNA), indicative of the proliferative state of cells, was reduced synchronously with PKCmu as the hyperplastic state of the neonatal tissue declined. In epidermal mouse keratinocytes, fractionated according to their maturation state, PKCmu expression was restricted to PCNA-positive basal-cell fractions. In primary cultures of those cells, growth arrest and induction of terminal differentiation by Ca2+ resulted in strongly reduced PKCmu expression, concomitantly with the loss of PCNA expression. Treatment of **PMK**-RI keratinocytes with 100 nM of the mitogen 12-O-tetradecanoylphorbol-13-acetate (TPA) resulted in activation of PKCmu, reflected by translocation from the cytosolic to the particulate fraction and by shifts in electrophoretic mobility. DNA synthesis was significantly **inhibited** by the PKCmu **inhibitor** Goedecke 6976, while Goedecke 6983 did not **inhibit** PKCmu. Carcinomas generated according to the 2-stage carcinogenesis protocol in mouse skin consistently exhibited high levels of PKCmu. These data correlate PKCmu expression with the proliferative state of murine keratinocytes and point to a role of PKCmu in growth stimulation. A correlation between PKCmu expression and enhanced cell proliferation was also observed for NIH3T3 fibroblasts transfected with and overexpressing human PKCmu.

L48 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1998052312 MEDLINE
DOCUMENT NUMBER: 98052312 PubMed ID: 9392419
TITLE: Post-translational regulation of mevalonate kinase by intermediates of the cholesterol and nonsterol isoprene biosynthetic pathways.
AUTHOR: Hinson D D; Chambliss K L; Toth M J; Tanaka R D; Gibson K M
CORPORATE SOURCE: Institute of Metabolic Disease, Baylor University Medical Center, Dallas, TX 75226, USA.
SOURCE: JOURNAL OF LIPID RESEARCH, (1997 Nov) 38 (11) 2216-23.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980130

AB To assess the potential for feedback **inhibition** by isoprene intermediates in the cholesterol and nonsterol isoprene biosynthetic pathway, we expressed human cDNAs encoding mevalonate kinase (MKase), **phosphomevalonate kinase** (PMKase), and mevalonate diphosphate decarboxylase (MDDase) as fusion **proteins** in Escherichia coli DH5alpha, and purified these **proteins** by affinity chromatography. Several phosphorylated and non-phosphorylated isoprenes were analyzed as inhibitors of the enzymes using a standard spectrophotometric **assay**. Of the three **proteins**, only MKase was inhibited through competitive interaction at the ATP-binding site. The intermediates studied (and their relative inhibitory capacity) were: geranylgeranyl-diphosphate (GGPP, C20) > farnesyl-diphosphate

(FPP, C15) > geranyl-diphosphate (GPP, C10) > isopentenyl-diphosphate (IPP, C5) > or = 3,3-dimethylallyl-diphosphate (DMAPP, C5) > farnesol (C15) > dolichol-phosphate (DP, C(80-100)). Mevalonate-diphosphate, geraniol, and dolichol were not inhibitors. Our data further define the spectrum of physiologic inhibitors of MKase, and provide the first evidence for feedback inhibition of MKase by a nonsterol isoprene produced by the branched pathway, dolichol-phosphate. These results provide additional evidence that MKase may occupy a central regulatory role in the control of cholesterol and nonsterol isoprene biosynthesis.

L48 ANSWER 8 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 3

ACCESSION NUMBER: 1996:427692 BIOSIS
DOCUMENT NUMBER: PREV199699158748
TITLE: Induction of early mevalonate pathway enzymes and biosynthesis of end products in potato (Solanum tuberosum) tubers by wounding and elicitation.
AUTHOR(S): Bianchini, Graciela M.; Stermer, Bruce A.; Paiva, Nancy L. (1)
CORPORATE SOURCE: (1) Plant Biol. Div., Samuel Roberts Noble Found., P.O. Box 2180, Ardmore, OK 73402 USA
SOURCE: Phytochemistry (Oxford), (1996) Vol. 42, No. 6, pp. 1563-1571.
ISSN: 0031-9422.
DOCUMENT TYPE: Article
LANGUAGE: English

AB In plants, several important classes of terpenoid compounds are synthesized via the mevalonate pathway. In addition to essential constitutive metabolites, potato (Solanum tuberosum L.) tubers synthesize antifungal sesquiterpenoid phytoalexins in response to fungal infection or arachidonic acid elicitation, and toxic steroid glycoalkatoids in response to wounding. The activity of the early pathway enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) has previously been shown to increase rapidly and then decrease in response to these stimuli. During an investigation of the possible post-translational control of this enzyme, it was found that the inclusion of the cysteine protease **inhibitors** leupeptin and E-64 (-(N-(L-3-trans-carboxyran-2-carbonyl)-L-leucyl)agmatine) in the enzyme extraction buffer increased nine-fold the total HMGR activity recovered in the microsomal fraction and greatly increased the ratio of microsomal to soluble activity. Incubation of microsomal HMGR preparations with soluble **protein** extracts, Mg-2+ and ATP caused an apparent **inhibition** of HMGR, consistent with published reports of post-translational inactivation of HMGR by phosphorylation. The apparent **inhibition** was completely reversed, however, by 5 mM mevalonate and was found to be an artefact caused by the presence of mevalonate kinase, the next enzyme in the pathway, in the soluble fraction. HPLC **assays** for mevalonate kinase and **mevalonate phosphate kinase** were developed and used to measure the activities of these enzymes following wounding and elicitation. While HMGR levels increased 30-fold following arachidonic acid treatment and 15-fold following wounding, mevalonate kinase and **mevalonate phosphate kinase** only increased two- to four-fold following these treatments, and the levels in arachidonic acid treated tubers were only 20-40% higher than in wounded tubers. While

HMGR levels are extremely low in untreated tissues, the activities of the two kinases are relatively high, suggesting that they do not serve as control points for the synthesis of terpenoids.

L48 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:53625 BIOSIS
DOCUMENT NUMBER: BA91:31906
TITLE: SITE OF CLOMAZONE ACTION IN TOLERANT SOYBEAN AND SUSCEPTIBLE COTTON PHOTOMIXOTROPHIC CELL SUSPENSION CULTURES.
AUTHOR(S): NORMAN M A; LIEBL R A; WIDHOLM J M
CORPORATE SOURCE: DEP. AGRONOMY, UNIVERSITY ILLINOIS, URBANA, ILL. 61801.
SOURCE: PLANT PHYSIOL (BETHESDA), (1990) 94 (2), 704-709. CODEN: PLPHAY. ISSN: 0032-0889.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Studies were conducted to **determine** the herbicidal site of clomazone action in tolerant-soybean (Glycine max [L.] Merr. cv Corsoy ((SB-M) and susceptible-cotton (Gossypium hirsutum [L.] cv Stoneville 825) (COT-M) photomixotrophic cell suspension cultures. Although a 10 micromolar clomazone treatment did not significantly reduce the terpene or mixed terpenoid content (microgram per gram fresh weight) of the SB-M cell line, there was over a 70% reduction in the chlorphyll (Chl), carotenoid (CAR), and plastoquinone (PQ) content of the COT-M cell line. The tocopherol (TOC) content was reduced only 35.6%. Reductions in the levels of Chl, CAR, TOC, and PQ indicate that the site of clomazone action in COT-M cells is prior to geranylgeranyl pyrophosphate (GGPP). The clomazone treatment did not significantly reduce the flow of [14C]mevalonate ([14C]MEV) (nanocuries per gram fresh weight) into CAR and the three mixed terpenoid compounds of SB-M cells. Conversely, [14C]MEV incorporation into CAR and the terpene moieties of Chl, PQ, and TOC in COT-M cells was reduced at least 73%, indicating that the site of clomazone action must be after MeV. Sequestration of clomazone away from the chloroplast cannot account for soybean tolerance to clomazone since chloroplasts isolated from both cell lines incubated with [14C] clomazone contained a similar amount of radioactivity (disintegrations per minute per microgram of Chl). The possible site(s) of clomazone **inhibition** include mevalonate kinase, **phosphomevalonate kinase**, pyrophosphomevalonate decarboxylase, isopentenyl pyrophosphate isomerase, and/or a prenyl transferase.

L48 ANSWER 10 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1987:446394 BIOSIS
DOCUMENT NUMBER: BA84:102232
TITLE: CHLOROPLAST AUTONOMY FOR THE BIOSYNTHESIS OF ISOPENTENYL DIPHOSPHATE IN GUAYULE PARTHENIUM-ARGENTATUM GRAY.
AUTHOR(S): REDDY A R; DAS V S R
CORPORATE SOURCE: DEP. BOTANY, SCH. BIOL. EARTH SCI., SRI VENKATESWARA UNIV., TIRUPATI 517 502, INDIA.
SOURCE: NEW PHYTOL, (1987) 106 (3), 457-464. CODEN: NEPHAV. ISSN: 0028-646X.
FILE SEGMENT: BA; OLD

LANGUAGE: English

AB Purified chloroplasts (80% intact) with a photosynthetic activity of 195 .mu.mol O2 mg chlorophyll-1 h-1 were prepared from the leaves of guayule. The activities of phosphoglyceromutase, enolase and pyruvate kinase were estimated in the purified chloroplasts and compared with those of Phaseolus radiatus Roxb. Activity of the pyruvate dehydrogenase complex (PDC) in the chloroplasts of guayule (4.48 nkat mg **protein**-1) was substantially higher than the PDC activity of Phaseolus (2.82 nKat mg **protein**-1). Incorporation of carbon from the added labeled carbon compounds, [14C]bicarbonate, [2-14C]pyruvate and [U-14C]-3-phosphoglycerate into isopentenyl diphosphate (IDP) was significant, indicating the ability of the chloroplasts to utilize Calvin cycle intermediates for IDP biosynthesis via acetyl CoA and mevalonate. DCMU **inhibited** the incorporation of 14CO2 and [14C]pyruvate into IDP. Acetoacetyl CoA thiolase, HMG-CoA reductase, mevalonate kinase, **phosphomevalonate kinase** and pyrophosphomevalonate decarboxylase activity were localized in the isolated chloroplasts. It is believed that the chloroplasts in the leaf of guayule are autonomous for the biosynthesis of IDP and this is presumed to be dependent on photosynthetic energy and carbon flow.

L48 ANSWER 11 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1988:131721 BIOSIS
DOCUMENT NUMBER: BA85:66548
TITLE: STUDIES ON PIG LIVER MEVALONATE-5-DIPHOSPHATE DECARBOXYLASE.
AUTHOR(S): CHIEW Y E; O'SULLIVAN W J; LEE C S
CORPORATE SOURCE: SCH. BIOCHEM., UNIV. NEW SOUTH WALES, P.O. BOX 1, KENSINGTON, NSW 2033, AUSTRALIA.
SOURCE: BIOCHIM BIOPHYS ACTA, (1987) 916 (3), 271-278. CODEN: BBACAQ. ISSN: 0006-3002.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB A procedure in which three sequential enzymes of cholesterol biosynthesis, mevalonate kinase (ATP: (R)-mevalonate 5-phosphotransferase, EC 2.7.1.36), **phosphomevalonate kinase** (ATP: (R)-5-phosphomevalonate phosphotransferase, EC 2.7.4.2) and mevalonate-5-diphosphate decarboxylase (ATP: (R)-5-diphosphomevalonate carboxy-lyase (dehydrating), EC 4.1.1.33), from pig liver, could be purified in the one operation is described. Mevalonate kinase and **phosphomevalonate kinase** were utilized for the enzymic synthesis of mevalonate 5-diphosphate (both 1-14C-labelled and unlabelled), the substrate for mevalonate-5-diphosphate decarboxylase, using excess free ATP4-. A radioactive **assay** for the enzyme, based on the release of 14CO2 from [1-14C]mevalonate-5-diphosphate, was developed. The **assay** allowed reassessment of the metal and nucleotide specificity of the decarboxylase. ATP could be partially replaced by GTP and ITP, but no activity was observed with CTP, UTP or TTP. Apparent activation of the enzyme by ATP4- was observed as found for mevalonate kinase (C. S. Lee and W.J. O'Sullivan (1983) Biochim. Biophys. Acta 747, 215-224) and **phosphomevalonate kinase** (C.S. Lee and W.J. O'Sullivan (1985) Biochim. Biophys. Acta 839, 83-89). The presence of 1 mM excess free ATP4-, above that complexed as the substrate MgATP2-, decreased the Km for MgATP2- from 0.45 mM to 0.15 mM. MgADP- was shown to act as a

competitive **inhibitor** with respect to MgATP2-.

L48 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 4

ACCESSION NUMBER: 1987:4954 BIOSIS
DOCUMENT NUMBER: BA83:4954
TITLE: QUANTITATIVE ROLE OF DIFFERENT EMBRYONIC TISSUES IN MEVALONATE METABOLISM BY STEROL AND NONSTEROL PATHWAYS RELATIONSHIP WITH ENZYME ACTIVITIES OF CHOLESTEROGENESIS.
AUTHOR(S): MARCO C; GONZALEZ-PACANOWSKA D; SEGOVIA J L; GARCIA-PEREGRIN E
CORPORATE SOURCE: DEP. BIOCHEM., UNIV. GRANADA, GRANADA, SPAIN.
SOURCE: BIOCHIM BIOPHYS ACTA, (1986) 878 (2), 238-242. CODEN: BBACAQ. ISSN: 0006-3002.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB 3-Hydroxy-3-methylglutaryl-CoA reductase, mevalonate kinase, **mevalonate**-5-**phosphate kinase** and mevalonate-5-pyrophosphate decarboxylase activities have been **determined** in brain, liver, intestine and kidneys from 19-day-old chick embryo. Levels of brain reductase and decarboxylase were clearly higher than those found in the other tissues **assayed**. However, only small differences were observed in the activity of both kinases among the different tissues. Mevalonate metabolism by sterol and nonsterol pathways has been investigated in chick embryo at the same developmental stage. Mevalonate incorporation into total nonsaponifiable lipids was maximal in liver, followed by intestine, brain and kidneys. The shunt pathway of mevalonate not leading to sterols was negligible in both brain and liver, while a clear CO2 production was observed in intestine and kidneys. Sterols running in TLC as lanosterol and cholesterol were the major sterols formed from mevalone by brain and kidney slices, while squalene and squalene oxide(s) were found observed in chick embryo intestine. The importance of free and esterified cholesterol accumulation in the different tissues on the **inhibition** of cholesterogenic activity is discussed.

L48 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1984:201638 BIOSIS
DOCUMENT NUMBER: BA77:34622
TITLE: AN IMPROVED PURIFICATION PROCEDURE AN ALTERNATIVE **ASSAY** AND ACTIVATION OF MEVALONATE KINASE EC-2.7.1.36 BY ATP.
AUTHOR(S): LEE C S; O'SULLIVAN W J
CORPORATE SOURCE: SCH. BIOCHEM., UNIV. NEW SOUTH WALES, P.O. BOX 1, KENSINGTON, NSW 2033, AUST.
SOURCE: BIOCHIM BIOPHYS ACTA, (1983) 747 (3), 215-224. CODEN: BBACAQ. ISSN: 0006-3002.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB An improved procedure for the purification of pig liver mevalonate kinase is described. A high-voltage electrophoresis **assay** was developed for mevalonate kinase. The procedure separates mevalonate from phosphomevalonate and also from diphosphomevalonate so that it can be used to measure the subsequent enzyme, **phosphomevalonate kinase** (EC 2.7.4.2). The

assay allowed the reassessment of the metal ion and nucleotide specificity of the pig liver enzyme. Some of the previously reported properties reflected those of the enzymes in the coupling **assay** rather than mevalonate kinase itself. A series of compounds were **tested** as activators or **inhibitors** of mevalonate kinase. ATP4-, arsenate and, to a smaller extent, Pi activated the enzyme. At fixed MgATP2- (1 mM) concentrations the activation of mevalonate kinase by free ATP4- at pH 8.0 was observed at concentrations up to 10-fold that of MgATP2- before causing any **inhibition**. The presence of free ATP4- resulted in a biphasic Lineweaver-Burke plot with apparent Km values for MgATP2- being 0.14 mM and 60 .mu.M, respectively. Fluorescence measurements were consistent with the notion that the binding of excess ATP4- to the enzyme caused a conformational change.

L48 ANSWER 14 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1980:264569 BIOSIS
DOCUMENT NUMBER: BA70:57065
TITLE: PIG LIVER PHOSPHO MEVALONATE KINASE 2. PARTICIPATION OF CYSTEINYL AND LYSYL GROUPS IN CATALYSIS.
AUTHOR(S): BAZAES S; BEYTIA E; JABALQUINTO A M; DE OVANDO F S; GOMEZ I; EYZAGUIRRE J
CORPORATE SOURCE: LAB. BIOQUIM., INST. CIENC. BIOL., UNIV. CATOL., CASILLA 114-D, SANTIAGO, CHILE.
SOURCE: BIOCHEMISTRY, (1980) 19 (11), 2305-2310. CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB **Phosphomevalonate kinase** from pig liver is inactivated by 5,5'-dithiobis(2-nitrobenzoate) and pyridoxal 5'-phosphate. The substrate phosphomevalonate protects the enzyme against inactivation by these reagents. Inactivation by 5,5'-dithiobis(2-nitrobenzoate) is complete and may be reverted by 2-mercaptoethanol or dithiothreitol. Experiments carried out with partially inactivated enzyme show no change in the kcat or in the apparent Km for the substrates, as compared with the native enzyme, indicating the existence of 2 populations of molecules, one intact and the other totally inactive. 5,5'-Dithiobis(2-nitrobenzoate) apparently reacts with the only cysteinyl residue of the enzyme and this residue is located in or near the active site. **Inhibition** by pyridoxal 5'-phosphate can be reverted, either by dialysis or by the addition of lysine, but not if the partially inactivated enzyme is treated previously with NaBH4, in agreement with the formation of a Schiff base between pyridoxal 5'-phosphate and an amino group of the enzyme. This is further supported by the appearance of an absorption band with a maximum at 325 nm in the enzyme treated with pyridoxal 5'-phosphate and NaBH4. Pyridoxal and pyridoxamine 5'-phosphate are weaker **inhibitors** than pyridoxal 5'-phosphate, suggesting a specific effect due to the phosphate and aldehyde groups. The enzyme is not completely inactivated by pyridoxal 5'-phosphate, even at a molar ratio of 350, or by a 2nd inactivation treatment after reduction with NaBH4. The partially modified enzyme shows a lower Km for phosphomevalonate than the native enzyme, suggesting that the reactive group is located near the binding site of phosphomevalonate. The lower Km may reflect an effect of the positive charge of the pyridoxal 5'-phosphate ring N, enhancing the binding of phosphomevalonate.

Values of 8.15 at 24.degree. C and 7.95 at 31.degree. C were **determined** for the pK of the reactive group. A .DELTA.Hi of 11.8 kcal/mol was estimated, in agreement with the values expected for an amino group. One amino group/active site is involved in the enzyme inactivation as shown by kinetic data. Quantification of the number of moles of pyridoxal 5'-phosphate bound/mole of enzyme is not conclusive but supports this assertion. This group may correspond to an .epsilon.-amino group of lysine.

L48 ANSWER 15 OF 16 MEDLINE on STN
ACCESSION NUMBER: 80020244 MEDLINE
DOCUMENT NUMBER: 80020244 PubMed ID: 226078
TITLE: **Inhibition** of rat liver mevalonate pyrophosphate decarboxylase and **mevalonate phosphate kinase** by phenyl and phenolic compounds.
AUTHOR: Shama Bhat C; Ramasarma T
SOURCE: BIOCHEMICAL JOURNAL, (1979 Jul 1) 181 (1) 143-51. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197911
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19791121

AB 1. Mevalonate pyrophosphate decarboxylase of rat liver is inhibited by various phenyl and phenolic acids. 2. Some of the phenyl and phenolic acids also **inhibited mevalonate phosphate kinase**. 3. Compounds with the phenyl-vinyl structure were more effective. 4. Kinetic studies showed that some of the phenolic acids compete with the substrates, mevalonate 5-phosphate and mevalonate 5-pyrophosphate, whereas others inhibit umcompetitively. 5. Dihydroxyphenyl and trihydroxyphenyl compounds and p-chlorophenoxyisobutyrate, a hypocholesterolaemic drug, had no effect on these enzymes. 6. Of the three mevalonate-metabolizing enzymes, mevalonate pyrophosphate decarboxylase has the lowest specific activity and is probably the rate-**determining** step in this part of the pathway.

L48 ANSWER 16 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1979:270539 BIOSIS
DOCUMENT NUMBER: BA68:73043
TITLE: **INHIBITION** OF RAT LIVER MEVALONATE PYRO PHOSPHATE DECARBOXYLASE EC-4.1.1.33 AND **MEVALONATE PHOSPHATE KINASE** EC-2.7.4.2 BY PHENYL AND PHENOLIC COMPOUNDS.
AUTHOR(S): SHAMA BHAT C; RAMASARMA T
CORPORATE SOURCE: DEP. BIOCHEM., INDIAN INST. SCI., BANGALORE-560 012, KARNATAKA, INDIA.
SOURCE: BIOCHEM J, (1979) 181 (1), 143-152. CODEN: BIJOAK. ISSN: 0306-3275.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Mevalonate pyrophosphate decarboxylase [EC 4.1.1.33] of rat liver is **inhibited** by various phenyl and phenolic acids. Some phenyl

and phenolic acids also **inhibited mevalonate phosphate kinase** [EC 2.7.4.2]. Compounds with the phenyl-vinyl structure were more effective. Kinetic studies showed that some of the phenolic acids compete with the substrates, mevalonate 5-phosphate and mevalonate 5-pyrophosphate, whereas others **inhibit** uncompetitively. Dihydroxyphenyl and trihydroxyphenyl compounds and p-chlorophenoxyisobutyrate, a hypocholesterolemic drug, had no effect on these enzymes. Of the 3 mevalonate-metabolizing enzymes, mevalonate pyrophosphate decarboxylase has the lowest specific activity and is probably the rate-**determining** step in this part of the pathway.

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, USPATFULL' ENTERED AT 12:29:14 ON 11 AUG 2003)

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L49         246 S "ROSAM!ND J"?/AU
L50         119 S "SCHNELL N"?/AU
L51           7 S L49 AND L50
L52           2 S (L49 OR L50) AND L37
L53           7 S L51 OR L52
L54           2 DUP REM L53 (5 DUPLICATES REMOVED)
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- Author (s)

L54 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2001:152820 HCAPLUS
DOCUMENT NUMBER: 134:204352
TITLE: Cloning, expression, characterization and therapeutic uses of **phosphomevalonate kinase** from Candida albicans
INVENTOR(S): **Rosamond, John David Charles; Schnell, Norbert Friedemann**
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001014533	A2	20010301	WO 2000-GB3100	20000815
WO 2001014533	A3	20010927		
W: JP, MG, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1212431	A2	20020612	EP 2000-951744	20000815
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003507060	T2	20030225	JP 2001-518847	20000815

PRIORITY APPLN. INFO.: GB 1999-19766 A 19990821
WO 2000-GB3100 W 20000815

AB The invention relates to the **phosphomevalonate kinase** (**PMK**) gene (ERG8 gene) from Candida albicans (C. albicans), to methods for its expression yielding **phosphomevalonate kinase** protein, to novel hybrid organisms for use in such expression methods, to methods for purifn. of the protein, to methods and tools for diagnosing C. albicans infection and to assays for identifying inhibitors of the enzyme which inhibitors have potential as anti-fungal agents. The authors

have successfully cloned the ERG8 gene from C. albicans and detd. its full length nucleotide sequence and corresponding polypeptide sequence. The coding DNA sequence of the C. albicans ERG8 gene isolated is 1299 nucleotides in length and the corresponding protein sequence is 433 amino acids in length.

L54 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2000:690177 HCAPLUS
DOCUMENT NUMBER: 134:142394
TITLE: Evaluation of the CaMAL2 promoter for regulated expression of genes in Candida albicans
AUTHOR(S): Backen, Alison C.; Broadbent, Ian D.; Fetherston, Richard W.; **Rosamond, John D. C.**; **Schnell, Norbert F.**; Stark, Michael J. R.
CORPORATE SOURCE: University of Manchester, Manchester, MI3 9PT, UK
SOURCE: Yeast (2000), 16(12), 1121-1129
CODEN: YESTE3; ISSN: 0749-503X
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An expression vector (CIp10-MAL2p) for use in Candida albicans has been constructed in which a gene of interest can be placed under the control of the CaMAL2 maltase promoter and stably integrated at the CaRP10 locus. Using this vector to express the Candida URA3 gene from the CaMAL2 promoter, we have demonstrated tight regulation of CaURA3 expression by carbon source. Thus under conditions when the CaMAL2 promoter is not induced, expression of Candida URA3 was unable either to complement a C. albicans ura3 mutation or to confer sensitivity to 5-fluoroorotic acid, a compd. which is highly toxic to URA3 strains. Since Candida albicans is an obligate diploid organism, anal. of gene function requires manipulation of both copies of any gene of interest. Our expression vector provides a strategy by which the remaining copy of a gene of interest can be placed under CaMAL2 promoter control in a strain where the first copy has been deleted, permitting anal. of gene function by manipulation of carbon source. CIp10-MAL2p should therefore provide a useful means for functional anal. of genes in C. albicans. We have used this strategy with C. albicans DPB2 to demonstrate that the gene is essential and that loss of function leads cells to adopt a hypha-like morphol. as they cease proliferation.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'HOME' ENTERED AT 12:36:29 ON 11 AUG 2003